STUDY 1 OF 3

PROTOCOL

Cardiovascular Effects of Ultrafine Particles in Genetically Susceptible Subjects (CUSP)

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I. HYPOTHESES

Exposure to particulate matter (PM) air pollution is associated with increased pulmonary and cardiovascular mortality and morbidity. The mechanisms and genetic determinants of susceptibility represent gaps in our understanding of the health effects of PM air pollution. Ultrafine particles (UFP) are of concern because of their high fractional deposition in the distal airways and alveoli of the lung when inhaled, their ability to enter cells and organelles by diffusion, and their high surface area and oxidant potential.

We propose that exposure to ambient UFP alters both airway and vascular function in susceptible people, by delivering an oxidative burden to the lung epithelium and endothelium, with generation of reactive oxygen (ROS) and nitrogen species (RNS). These free radicals reduce intravascular nitric oxide (NO) bioavailability both locally and systemically, via chemical inactivation and reduced synthesis of NO, with subsequent impairment in circulatory nitrite delivery.

In the lung, this causes reductions in airway function, pulmonary vasoconstriction, and reduced pulmonary capillary blood volume. In the peripheral vasculature, reduced NO bioavailability impairs endothelial function. These effects, in turn, are expected to alter

hemodynamic measurements, including blood pressure, cardiac stroke volume, and/or cardiac output. Endothelial injury and NO depletion may activate platelets and generate pro-coagulant circulating microparticles, increasing the risk for thrombosis in patients with severe vascular disease. We hypothesize that people with genetically based reduction in anti-oxidant defenses are most likely to experience these effects.

Our study will combine physiologic measures of vascular and cardiac function with novel markers of NO bioavailability and transport to test the following hypotheses:

1. *Ambient UFP exposure impairs pulmonary & systemic vascular function, in part by altering NO transport and bioavailability.*
2. *Dysfunction in selected oxidant defense genes increases susceptibility to the pulmonary and cardiovascular effects of UFP.*
3. *In susceptible subjects, UFP pulmonary and cardiovascular effects will be related to markers of systemic oxidative stress.*

II. PURPOSE OF THE STUDY AND BACKGROUND

It is now well established that air pollution contributes to morbidity and mortality from pulmonary and cardiovascular disease. Increases in ambient particulate matter (PM) are associated with cardiovascular mortality, acute myocardial infarction, congestive heart failure, arrhythmias, and stroke (Frampton and Utell 2006). The American Heart Association recognizes air pollution as a risk factor for cardiovascular disease. Long-term exposure to fine particle air pollution has been shown to reduce life expectancy, and a recent study (Pope et al. 2009) found that reductions in fine PM levels of 10 $\mu g/m^3$ in US metropolitan areas were associated with an increased life expectancy of 0.61 years. Reductions in air pollution accounted for as much as 15% of the overall increase in life expectancy during the study period. Understanding the susceptibility to and mechanisms of the pulmonary and cardiovascular effects of particulate air pollution will assist in developing protective strategies, with the potential to improve public health.

A major goal of our laboratory is to understand the **determinants of susceptibility to exposure to ultrafine particle air pollution**. The **genetic** determinants of susceptibility represent a major gap in our knowledge. Several epidemiological studies have found associations between specific gene polymorphisms and effects of PM exposure, especially among genes that are involved in defense against oxidative stress. However, **confirmation in clinical inhalation studies is needed to determine causality and test mechanistic hypotheses.**

Ultrafine particles (UFP, <100 nm diameter) may be particularly important with regard to cardiovascular effects because of their potential for evading pulmonary clearance mechanisms, and for entering the lung interstitial and vascular spaces. UFP have a high specific surface area and carry an increased burden of reactive oxygen species (ROS), compared with larger particles. We have shown that inhalation of environmentally relevant concentrations of ultrafine elemental carbon particles altered both pulmonary and systemic vascular function in healthy subjects (Frampton et al. 2006; Pietropaoli et al. 2004; Shah et al. 2008). In subjects with type 2 diabetes, carbon UFP inhalation caused platelet activation (Frampton et al. 2007), increases in heart rate, and decreases in heart rate variability. We have now completed a study of inhalation of concentrated ambient UFP in healthy subjects at rest, and found transient increases in diastolic and mean blood pressure after UFP, increases in platelet-leukocyte conjugates, and delayed reductions in lung function (FEV_1), compared with clean air exposure. There is considerable

variability in these effects among subjects, not explained by differences in gender, age, or other clinical characteristics. Genetic differences likely contribute to the observed variability.

We now propose an integrated hypothesis for UFP vascular effects that incorporates our and others' observations, and provides mechanistic plausibility for the observed associations between PM exposure and cardiovascular events. We propose that exposure to ambient UFP presents an increased burden of ROS to the vascular endothelium, reducing NO bioavailability, impairing endothelial function in both the pulmonary and systemic vascular beds, and enhancing blood coagulation via platelet activation and generation of pro-coagulant circulating microparticles. We further propose that people with genetically determined impairment of antioxidant defense enzyme function will be more susceptible to these effects. Our study will combine physiologic measures of vascular and cardiac function with novel markers of nitric oxide (NO) bioavailability and transport.

III. CHARACTERISTICS OF THE RESEARCH POPULATION

A. Number of Subjects:

36 subjects will be needed to complete the study. 12 of the 36 subjects will be GSTM1 null, 12 subjects will be Nrf2-617A/C, and 12 subjects will be wild type for both genes (GSTM1+ and Nrf2-617C/C). We estimate approximately 80 subjects will be enrolled in the study and screened to achieve this.

B. Gender of Subjects:

Both genders will participate.

C. Age of Subjects:

The age of the subjects will be 18 to 60 years.

D. Racial and Ethnic Origin:

No subject will be excluded from this study on the basis of gender, race, or ethnic group. Women of childbearing potential will not be excluded unless they are pregnant or breast-feeding.

The Table below shows the planned enrollment of subjects according to the categories indicated. This reflects the population distribution in the Rochester area. This representation will be achieved through differential acceptance of volunteers, and if necessary, through specific recruitment of under-represented groups.

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not Hispanic	Hispanic	White, not Hispanic	Other or Unknown	Total
Total	0	4	4	3	25		36

E. Inclusion Criteria:

Volunteers will be healthy, never-smokers with normal spirometry based on the standards published by Morris and co-workers (Morris et al. 1971).

F. Exclusion Criteria:

1. Any history of habitual smoking.
2. Marijuana smoking within the past 5 years.
3. Pregnancy.
4. Any history of significant organ impairment, chronic respiratory disease, ischemic heart disease, active psychiatric disorder or current drug or alcohol abuse.
5. Occupation involving regular, heavy dust or particle exposure, such as welding, mining, foundry work.
6. $FEV_1 < 75\%$ of predicted at baseline screening.
7. Subjects with atopy or allergic rhinitis will not be excluded as long as they do not require regular treatment with antihistamines or systemic steroids.
8. Subjects on certain prescription medications such as prednisone or statins will be excluded. Use of other medications will be considered on an individual basis. Subjects will not be asked to discontinue prescription medications for the purposes of this study.
9. Hypertension (blood pressure higher than 140/90 mmHg or on antihypertensive medication).

Subjects must be able to avoid the medications/supplements listed in this table for the time indicated in each column heading:

1 WEEK	1 DAY TO 1 WEEK
Non-steroidal anti-inflammatory drugs such as ibuprofen, naproxen, aspirin Supplemental vitamins Antihistamines Anti-oxidants Fish oil Niacin Arginine Over-the counter decongestants	Sildenafil (Viagra) (36 hours) Vardenafil (Levitra) (36 hours) Tadalafil (Cialis) (87 hours)

G. Vulnerable Populations:

Students at the University of Rochester and other area campuses will be allowed to participate in this study; however, students and staff specifically supervised or evaluated by one of the investigators will be excluded.

H. Restrictions on Recruited Subjects:

Subjects will be asked to avoid caffeine and ingest a low-nitrate diet on study days, starting the evening before the overnight visit (Visits 2, 4). Subjects will be asked to avoid strenuous exercise and heavy lifting on study days, starting the day before the overnight visit (Visits 2, 4). Subjects will not be studied within six weeks of a respiratory infection.

IV. METHODS AND PROCEDURES

A. Protocol

This study has a double-blind, randomized, controlled, crossover design. Each subject will have two exposures (clean air and particles) and a total of 5 visits, spanning about 6 weeks, with each exposure separated by at least 3 weeks. Only the person operating the exposure equipment will know which exposure is being given. The order of giving air or particles first will be chosen at random. Randomization of exposure order will be performed by the Department of Biostatistics and Computational Biology, and will be delivered as a set of envelopes to the exposure engineer prior to initiating the study.

Visit 1 is a screening day. Subjects will provide written informed consent; complete a standardized questionnaire for assessment of respiratory symptoms, medical and smoking history; and undergo a physical examination, spirometry, and a 12-lead ECG to exclude clinically evident coronary artery disease. At the time of screening, blood will be obtained for CBC, SMA-14, fasting lipid profile, hemoglobin A1C, and genetic testing. Premenopausal women will be screened for pregnancy. Subjects will be counseled in the low-nitrate diet by the CRC dietician. This visit is estimated to take 2-3 hours.

Blood drawn for genotyping will be sent to the Functional Genomics Center (FGC) at the University of Rochester Medical Center, under the direction of Dr. Stephen Welle. For GSTM1, the assay consists of polymerase chain reaction (PCR) amplification of exons 4 and 5 of the GSTM1 allele. The common polymorphism is a gene deletion. The presence of the PCR product indicates that the subject has of one or more copies of the gene. In each case concomitant amplification of the CYP1A1 gene will be done as a positive control to ensure that the lack of a GSTM1 product (GSTM1 null subjects) reflects the gene polymorphism rather than degraded DNA or presence of material inhibiting the PCR reaction. The PCR amplification of CYP1A1 results in a 312-bp product that is easily visualized after agarose gel electrophoresis in the presence or absence of the GSTM1 273-bp PCR product.

On a separate day (**Visit 2**), subjects will be admitted to the CRC at 11:30 am on the day before the first exposure. They will have been on a low-nitrate diet and avoiding caffeine since the evening meal the day before admission. They will be given lunch on the CRC. At 12:30 pm, they will undergo the following procedures: pregnancy test for pre-menopausal women, vital signs (blood pressure, heart rate and pulse oximetry), a symptom questionnaire, urine collection,

spirometry, phlebotomy (50 mL from a vein and 10mL from an artery), impedance cardiography, reactive hyperemia, diffusing capacity of the lung for NO (DLNO), diffusing capacity of the lung for carbon monoxide (DLCO), and measurement of lung volume. These procedures will take about 3 hours. Subjects will be given dinner that evening, and will stay on the CRC overnight.

The following morning the subject will have breakfast at 6:30 am. At 7:15 am the subject will be transported by wheelchair to the human exposure facility in the basement of the Kornberg Medical Research Building. The exposure to either clean, filtered air or concentrated UFP will occur from 7:45 am to 9:45 am, inside an air-tight, air-conditioned plexiglas chamber (6 x 5 x 3.5 feet, 98 cubic feet). The chamber will be at negative pressure, approximately 12 cm H_20 relative to atmospheric, which is necessary to draw air flow through the concentrator. Exposures will be at rest. An investigator or trained technician will directly observe the subject throughout the exposure.

Immediately after the exposure, vital signs will be recorded (blood pressure, heart rate and pulse oximetry) and the subject will complete a symptom questionnaire. The subject will then be transported by wheelchair back to the CRC to perform spirometry. Lunch will be provided at 11:30 am. At 12:30 pm, the same procedures will be performed as on the previous day: vital signs (blood pressure, heart rate and pulse oximetry), a symptom questionnaire, urine collection, spirometry, blood draw (50 mL from a vein and 10 mL from an artery), impedance cardiography, reactive hyperemia, DLNO, and DLCO. At the completion of these tests, the subject will leave the CRC. The subject will be instructed to remain on the low-nitrate diet and avoid caffeine and strenuous exercise.

On **Visit 3** the subject will return the next morning at 08:00. The subject will undergo the same sequence of tests as on the previous day: vital signs (blood pressure, heart rate and pulse oximetry), a symptom questionnaire, urine collection, spirometry, blood draw (50 mL from a vein and 10 mL from an artery), impedance cardiography, reactive hyperemia, DLNO, and DLCO. At the completion of these tests, the subject will leave the CRC. This concludes the first exposure measurements.

On **Visit 4**, at least three weeks after Visit 2, the subject will return for the alternate exposure (air or UFP). Procedures on this day and on **Visit 5** will be identical to Visits 2 and 3. Completion of Visit 5 will conclude the subject's participation in the study.

B. Procedures

1. Exposures

Exposures will be conducted in the human exposure facility using the Harvard Ultrafine Concentrated Ambient Particle System (HUCAPS), located in the basement of the MRBX. The output of the concentrator is ducted through the wall from the HUCAPs; overflow and exhaled aerosol are vented outdoors via an exhaust system.

Ambient air will be taken in from a street adjacent to the exposure room (Kendrick Road) via a 12-inch diameter duct system. Our 2-hour exposures will take place in the morning to coincide with peak traffic-related particle counts, and thus allow us to specifically target traffic-related UFP. The HUCAPS concentrates UFP about 15-fold, which would provide exposures to particle numbers up to $10^6/cm^3$. This is in the range of peak particle numbers measured in the cab of a truck on a busy highway (Kittelson et al. 2001), and is an order of magnitude lower than the particle number used in our studies of laboratory-generated carbon UFP ($\sim 10^7/cm^3$).

The HUCAPS concentrates without significant distortion of the original particle size or composition, so the exposures will be representative of real-world ultrafine particle exposures. Particle number and mass concentrations and size distributions will be continuously monitored for the unconcentrated outdoor air, and for the concentrated aerosol in the exposure chamber. A portion of the concentrator output will be diverted to sampling filters, for subsequent measurement of chemical composition and ROS generation of the concentrated aerosol. The particle concentration and composition will vary daily, and these exposure-day measurements will be used to construct dose-response relationships, and determine particle sources based on chemical composition.

2. Spirometry

Spirometry is a routine pulmonary functions test, in which subjects inhale to total lung capacity and perform a forced exhalation maneuver through a mouthpiece into a spirometer. The spirometer is connected to a computer that is able to plot flow-volume loops and calculate the volume of air exhaled in the first second (FEV_1). The maneuver is repeated three times and the largest of the values is used as the measurement. There are no significant risks associated with performing spirometry. Taking three deep breaths for the procedure can occasionally cause lightheadedness.

3. Measurement of Diffusing Capacity for Carbon Monoxide (DLCO)

The diffusing capacity for carbon monoxide (DLCO) is a standard test that measures the ability of the lungs to take up trace amounts of carbon monoxide across the epithelium of the tiny air sacs. Subjects inhale a single breath of a gas mixture containing 0.3% carbon monoxide, 10% helium, 21% oxygen, and the balance nitrogen, breath-hold for 10 seconds, and then exhale. The differences in the concentrations of helium and carbon monoxide in inhaled versus exhaled air allow the computer to calculate the DLCO. This test is performed on a daily basis as part of complete pulmonary function testing in the Clinical Pulmonary Function Laboratory. There are no significant risks associated with this test. Although carbon monoxide has adverse consequences when inhaled in sufficient quantities, the amount inhaled during this test is much less than that inhaled while smoking a cigarette, and has no physiological effects.

4. Measurement of Lung Volumes

Measurement of lung volumes is also part of routine pulmonary function testing, and will be performed once prior to the first exposure. The subject enters a body plethysmograph, a Plexiglas box with dimensions similar to a phone booth. By panting against a shutter, thoracic gas volume is measured non-invasively using an application of Boyle's law. The test requires up to 15 minutes and is a standard clinical test performed in pulmonary function laboratories.

5. Measurement of Diffusing Capacity for Nitric Oxide (DLNO)

The diffusing capacity for nitric oxide (DLNO) is measured using the same principles as for DLCO. The subject inspires to total lung capacity with gas enriched with 1 to 10 ppm NO, followed by a 3- to 5-second breath hold, and then exhales at 0.5 to 1.0 liters per second. This is repeated two times. NO in exhaled air is also measured. The subject breath-holds for 10 seconds

and then exhales at a constant expiratory flow rate while NO is measured. This is repeated two times.

6. Venous and Arterial Blood Draws

We hypothesize that systemic vascular effects of exposure to UFP will be reflected in reductions in arterial blood nitrite or its A/V gradient, and alter other markers of vascular function and inflammation. This will require simultaneous collection of venous and arterial blood.

Phlebotomy will be performed using standard techniques and universal precautions, by one of the investigators, one of the fellows in the Pulmonary and Critical Care Unit, or by one of the nurses or laboratory technicians in the Unit who has been trained to perform the procedure. The arterial blood draw will be performed only by a physician or other individual specifically trained and certified to perform this procedure. The amount of blood at each blood draw will be 50 ml or less from a vein in the arm and 10mL or less from the radial artery. The total amount of blood drawn over 3 days for any one exposure session will be 250 ml or less, with a maximum of 500 mL for the entire study (over more than 6 weeks). Subjects will have 3 venous and 3 arterial blood draws each week (one each day for 3 days) for any one exposure session.

In this study, serum and plasma samples will be saved for future research, using an alpha-numeric code to protect subject identity. Consent to this stipulation is a requirement for participation.

7. Reactive Hyperemia

RH of the forearm will be measured by venous occlusion plethysmography using the methodology we reported (Shah et al. 2008). RH is measured with the subject supine in a quiet room, at the same times of day for each exposure, and prior to any other measurements such as phlebotomy and spirometry because these studies may influence the measurements.

8. Impedance cardiography

Impedance cardiography (ICG) involves a noninvasive measurement of cardiac function. It converts changes in thoracic impedance to changes in volume over time. It is therefore used to track volumetric changes such as those occurring during the cardiac cycle. Skin electrodes are placed on the neck and sides of the chest. The impedance to a weak electrical current is measured over a period of five minutes. This is a standard method for monitoring cardiac function. There are no risks or complications associated with this procedure.

C. Data Analysis and Data Monitoring

We will take a sequential approach to the analysis, as follows.

1) The primary analysis will assess the effects of the experimental UFP exposures on the primary pulmonary and cardiovascular endpoints for all 36 subjects (the 3 groups combined); i.e., examine the concentration-related cardiopulmonary responses to UFP compared with air exposure. This analysis will include examination of the time course of the responses, and

interactions between treatment (pollutant exposure) and time. Because the ambient levels of UFP will vary day-to-day, exposures to the concentrated aerosols will vary, so we will examine relationships between UFP concentration (particle number and mass) and physiologic outcomes. We will also examine relationships between UFP oxidant capacity and the outcome measures.

2) Determine effects within and between the 3 subject groups (GSTM1 null, Nrf2 -617A/C, and wild type).

3) Determine **relationships** between the cardiovascular responses and: a) decrements in lung function, and b) systemic markers of oxidative stress. For example, if we find that UFP exposure reduces RH (a measure of systemic vascular responsiveness), and that this effect is greatest in the subjects with the greatest reduction in FEV_1, we can hypothesize that impairment in vascular function is mechanistically related to effects on airway inflammation. We expect that cardiovascular responses will be significantly related to oxidative stress, but not to decrements in lung function.

All data will be thoroughly checked for outliers and other possible rogue observations. Plots will be generated showing means and standard deviations over different exposure conditions for all subjects and for the three groups of subjects separately. Formal analyses will be performed using analysis of variance, including terms for subjects and for exposures. Should residual plots indicate that the assumptions underlying analysis of variance (additivity, homoscedasticity, normality of errors) not be satisfied, consideration will be given to the use of transformations (e.g. the logarithm, reciprocal, or square roots), or the use of an appropriate nonparametric procedure (e.g. Kruskal-Wallis). To assess the effect of the acute exposures under the control of the investigator, and which will be "nested" within subjects (each subject experiencing each of the two exposures), inference will be based on a model including terms for subjects and exposures, i.e. on within-subject variability. Confidence intervals for prespecified contrasts of interest will be constructed in the usual way. Comparisons between the three groups of subjects, and tests of differential effects of exposure among the three groups, will be based on between subjects variability.

Statistical analyses will be carried out in SAS version 9.1. All P-values will be two-sided, and a level of 5% will be required for statistical significance. Each outcome variable will be examined separately, but we will check for consistency of response across outcomes and for correlations between them. Because of the multifaceted nature of these studies, a fairly large number of significance tests will be performed. Our strategy in interpreting the results will rely on the pattern of significance tests, on concordant effects among biologically related variables, concentration-response relationships, and biological plausibility rather than the individual p

Table 1. Effect sizes for within subject analysis

Measure	Overall Mean	Effect Size (%), n=36	Effect Size (%), n=12
FEV_1	3.48	0.22	0.40
Mean BP	97.5	5.7	10.2
DLCO	27.8	4.6	7.9
Vc	88.8	15.7	27.1
RH peak flow	37.5	14.7	25.4
NO_2^- (venous)	172.3	25.2	43.4
CI	2.97	4.2	7.3%
VU_{NO}	53.9	11.9	20.6
VL_{NO}	168.1	20.7	35.7
Platelet CD62P	63.7	6.3	8.5
Plat-Mono conj	48.0	13.8	18.7

values. Results for the primary endpoints will be weighted the most heavily in data interpretation, and secondary endpoints will be interpreted insofar as they support or reject the primary hypotheses.

Sample Size Considerations

We have examined data from our previous studies measuring airways function (FEV_1), mean blood pressure (BP), pulmonary vascular function (DLCO, Vc), peripheral vascular function (RH, NO_2^-), cardiac index (CI) measured by impedance cardiography, airway NO exchange (VU_{NO}, VL_{NO}), and platelet activation (platelet CD62P and platelet-monocyte conjugates). For DLCO, 93% of the total variance was explained by subject differences, for each of the other measures the fractions were closer to 50%.

Table 1 shows effect sizes, for all 36 subjects and for each group of 12 subjects, detectable with 80% power, based on within subject variability. For simplicity, we have focused on a single prespecified contrast between two exposure levels (e.g. air vs. UFP exposure), using the fitted two-way analysis of variance model. Effect sizes are expressed as percentages of the baseline values. We obviously have power for detecting smaller effect sizes in the whole group of 36 subjects, and this will be our primary analysis. However, we expect that effects will be driven by one or both of the genetically susceptible groups, so will likely see larger effect sizes in the susceptible groups.

Table 2 gives the corresponding effect sizes for analyses comparing two groups, e.g. the normal subjects with those exhibiting the GSTM1 polymorphism.

Table 2. Effect sizes for group comparisons

Measure	Overall Mean	Effect Size (%)
FEV_1	3.48	30.6
Mean BP	97.5	12.6
DLCO	27.8	33
Vc	88.8	35
RH peak flow	37.5	30.5
NO_2^- (venous)	172.3	34.6
CI	2.97	17.7
Platelet CD62P	63.7	26.5
Plat-Mono conj	48.0	43.9

D. Data Storage and Confidentiality

Data will be recorded in bound laboratory books and transferred to and stored in a desktop computer using Excel software. Only the investigators and technicians directly involved in data acquisition and analysis will have access to the data. Samples and data will be coded to protect the identity of the subjects. Computers and data books will be stored in a locked laboratory.

V. RISK/BENEFIT ASSESSMENT

A. Risk Category

This research presents greater than minimal risk to the subjects.

B. Potential Risks

1. Exposures

It is very unlikely that these exposures to concentrated outdoor particles will cause symptoms or clinically important effects in healthy subjects. We have previously completing a study of concentrated UFP exposure in healthy subjects (RSRB # 13401) and in healthy subjects with asthma (RSRB#2467), and there have been no symptoms or airway effects in those studies. The U.S. Environmental Protection Agency completed a study in healthy subjects using the same Harvard ultrafine particle concentrator (Samet et al. 2007), and found no adverse effects. We previously exposed subjects with asthma to 10 $\mu g/m^3$ laboratory-generated carbon UFP, with intermittent exercise, without symptoms or airway effects. Our previous studies of exposure to UFP at 50 $\mu g/m^3$, with intermittent exercise, were without adverse effects. This study will be conducted at rest, which will further reduce the particle dose. In a separate study ("Inhaled particle characteristics and early lung effects," RSRB #8126), healthy subjects have been exposed to ultrafine and fine zinc oxide particles at a concentration of 500 $\mu g/m^3$ without adverse effects. Previous human studies of exposure to fine carbon particles found no clinical effects of exposure to 250 $\mu g/m^3$ for 1 hour or 500 $\mu g/m^3$ for 2 hours (Beckett et al. 2005). The National Ambient Air Quality Standard for outdoor particulate matter in the air ($PM_{2.5}$) is 65 $\mu g/m^3$, averaged over 24 hours.

There is a small, theoretical risk of precipitating a cardiac event in persons with severe coronary artery disease. Therefore, all subjects will be screened for coronary artery disease as part of the history and physical examination, and subjects will have a screening ECG read by a cardiologist prior to exposure. Nevertheless, it is possible that subjects recruited for this study could have clinically silent cardiovascular disease, that might not be detected by the screening examination and ECG. We feel that the risk for precipitating a cardiac event in these exposures is extremely small, even for a subject with unrecognized coronary artery disease. First, the particles used in this study will be outdoor particles similar to what people breathe every day. The number concentrations will be higher than people usually inhale in Rochester, but will be similar to what people breathe when driving on a busy highway, or working in certain occupations.

Second, all exposures will be conducted at rest, as opposed to some of our previous studies in healthy subjects, which have involved exercise. Thus, the actual dose of particles to the lung will be lower in this study, and the cardiovascular stress of exercise will be absent. Finally, the risk of cardiovascular events associated with outdoor air particles is relatively small, and has required studies of millions of people to detect. While this risk is important from a public health standpoint, the net increase in risk for individuals on any given day of exposure remains very small. For example, Peters et al. (Peters et al. 2001) found, in a study of residents in the Boston area, an odds ratio for MI of approximately 1.3 associated with an increase in air pollution from the cleanest days to the worst days. The age-adjusted incidence of first acute MI for adult males is approximately 10 per 1,000 person-years, or 10 per 365,000 person-days. Thus, according to the Peters data, the risk of having a heart attack related to the worst air pollution day in Boston would increase from 1 in 36,500 to 1 in 28,077. The risk would be lower for people without clinical evidence of coronary artery disease. Given that the exposures used in this study are for only 2 hours rather than a whole day, the risk of precipitating a cardiovascular event is extremely small.

2. Pulmonary Function Tests

These tests are performed on a daily basis in the pulmonary function laboratory, and are essentially without significant risk. Taking three deep breaths for spirometry can occasionally cause lightheadedness.

3. Measurement of DLNO

Inhalation of high concentrations of NO can be toxic to the lungs; however, the maximal inhaled level of 10 ppm of NO for only 1 to 3 breaths performed during this measurement is well below accepted toxic levels. For example, the threshold limits for exposure to nitric oxide published by the National Institutes of Occupational Safety and Health (NIOSH), the Occupational Safety and Health Administration (OSHA), and the American Conference of Government Industrial Hygienists is 25 ppm for 15 minutes to 8 hours per day (Lehnert 1993). Normal humans have 23 ppm of NO in the paranasal sinuses (Lundberg et al. 1994). We have found no adverse effects of performing these measurements in our previous protocols (RSRB #07121, 08006, 08293, 13401, 24667).

4. Blood Draws

The risks of drawing blood are minimal. Vasovagal syncope can occur, therefore, patients will be kept supine during phlebotomy. Subjects can also experience discomfort and/or bruising at the venipuncture site. More serious complications such as thrombophlebitis or infection, which can occur with indwelling intravenous catheters, are extremely unusual with simple phlebotomy. Obtaining blood from the radial artery is routinely performed in a variety of clinical settings to assess gas tensions and other parameters in arterial blood. The risks are minimal. The most notable potential side effects are self-limited pain, bleeding, or bruising at the puncture site. These risks are minimized by use of small gauge needles for arterial puncture and maintenance of firm manual pressure over the puncture site until hemostasis is visibly achieved. Like phlebotomy, vasovagal syncope is a possible but rare complication, and blood sampling can worsen pre-existing anemia. Other complications, (e.g., thrombophlebitis or infection) are extremely rare.

5. Reactive Hyperemia

Subjects may experience tingling of the hand or even brief numbness while the blood pressure cuff is inflated.

C. Protection against Risks

The Principal Investigator will be responsible for safety monitoring, and for the reporting of any adverse events to the RSRB and the CRC.

The subject will be under direct observation by a trained investigator (usually the engineer running the exposure) at all times during the exposure. Monitoring facilities provide continuous measurements of particle concentrations. Symptoms and sensitive measurements of pulmonary function will be monitored before and after exposure. Exposures will be discontinued if any adverse symptoms occur. All subjects will remain in the CRC for approximately 6 hours after exposure and symptoms will be assessed before discharge. Finally, subjects will return approximately 24 and 48 hours after each exposure to assess possible delayed effects.

The human exposure facility is located in the MRBX, a short walk from Strong Memorial Hospital. Physician availability is assured at all times.

For arterial puncture, an Allen's test will be performed prior to radial artery puncture, to ensure adequate blood flow to the hand. Also, investigators will apply firm manual pressure over the radial artery until hemostasis is assured.

D. Potential Benefits to the Subjects

There are no anticipated benefits to the subjects.

E. Alternatives to Participation

The alternative to participation in this study is not to participate.

VI. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT/ASSENT

A. Method of Subject Identification and Recruitment

Healthy, nonsmoking subjects will be recruited using advertisements on local bulletin boards, Internet volunteer bulletin boards (http://rochester.craigslist.org/vol/ or www.researchmatch.org), and in area newspapers. Potential participants will call or email our Study Coordinator who will describe the nature of the study to the subject. If the subject meets the criteria for the study and expresses willingness to participate, an appointment will be made for a visit to the Clinical Research Center (CRC).

B. Process of Consent

Consent will be obtained by the study coordinator or one of the investigators at the time of the initial visit. The consent form will be provided to the subject and the investigator will describe the study to the subject and will ask for and answer any questions. The subject will have the opportunity to take the consent form home to discuss it with family or advisors and to return with additional questions before deciding to participate. The consent form will then be signed by the subject and co-signed by the study coordinator or investigator. The subject will be given a copy of the signed consent.

C. Subject Competency

All subjects participating will be competent to provide consent, and competency will be determined by the investigator obtaining consent, using a brief mental status assessment.

D. Subject Comprehension

The subject's comprehension of the study will be assessed by the investigator, using questions designed to determine the subject's level of understanding of the study. After completing the presentation on the study and after the subject has read the consent form and asked questions, the subject will be asked to describe, in his or her own words, what will happen during the study.

E. Consent/Assent Form

Draft provided.

VII. FINANCIAL OBLIGATIONS AND INCENTIVES

A. Costs to the Subject

None.

B. Incentives for Participation

Subjects will be paid $100 after completing visit 1, $250 after completing visit 2, $100 after completing visit 3, $250 for completing visit 4, and $100 for completing visit 5, for a total of $800.

VIII. REFERENCES

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Shah AP, Pietropaoli AP, Frasier LM, Speers DM, Chalupa DC, Delehanty JM, et al. 2008. Effect of inhaled carbon ultrafine particles on reactive hyperemia in healthy human subjects. Environ Health Perspect 116: 375-380.

UNIVERSITY OF ROCHESTER
Research Subjects Review Board

RSRB No.: RSRB00030395

Date: Wednesday, December 09, 2009 15:58:24 Print Close

1. Study Identification Information. Protocol & Measures

1.1	*** Study Working (short) Title:** CUSP	*The "**short**" title will appear in your inbox to identify the study. The 'full' title (the official study title) may include too many characters to use as an identifier.*
1.2	*** Study Full Title:** Cardiovascular Effects of Ultrafine Particles in Genetically Susceptible Subjects	
1.3	* If the **Study Protocol** is available electronically, click **Add** to upload. Important: If you're revising or replacing the previously uploaded document, use the **Replace** link next to the file name. Do not delete any document after the study has been submitted to the RSRB.	***IMPORTANT!*** *Use the 'Add' button to upload new (i.e. previously not submitted) documents only. To make changes to a document that has already been submitted to the RSRB, use the 'Replace' link.*

name	Revision	Modified Date
CUSP Protocol	0.04	11/23/2009 9:16 AM

Example: If the study has been submitted and the RSRB sends the application back to your 'Inbox' and asks (a) for you to add a Statistical section to the protocol and (b) that you include a separate consent form for control subjects, proceed as follows:

1. *Go to the protocol section (1.3) and use the 'Edit' link to upload the revised version of your protocol.*
2. *Go to the consent section (83) and use the 'Add' button to upload the not yet submitted consent form for control subjects.*

1.3.1 * Does the study involve the administration of any assessments (surveys, questionnaires, diaries) or measures of human behavior? yes

If **Yes**, click **Add** to upload the **measure**(s). Important: If you're revising or replacing the previously uploaded document, use the **Replace** link next to the file name. Do not delete any document after the study has been submitted to the RSRB.

name	Revision	Modified Date
Symptom Questionnaire - Exposure Day	0.02	11/18/2009 10:12 AM
Symptom Questionnaire - Non-Exposure Day	0.02	11/18/2009 10:12 AM
Health Questionnaire	0.01	11/18/2009 10:11 AM

Typical examples of measures or assessments may include surveys/ questionnaires, interview scripts or behavioral assessments.

1.4

Principal Investigator	HSPP/EPRP	Expiration Date
* Mark Frampton	10120204	1/28/2010

Only the PI can "Submit" this application

Note: The HSPP/EPRP number and the expiration date will not be updated until the current form is being saved.

1.5 **Co-Principal Investigator(s):** (*Individuals who share full responsibility for the study with the Principal Investigator*)

Last	First	Organization	HSPP/EPRP No.	Expiration Date

There are no items to display

A "Co- Principal Investigator" is an individual who has full responsibility for the study. NIH refers to such individuals as "multiple principal investigators" and states that such a person "is a full-fledged principal investigator who has responsibilities appropriate to that role."

At the University of Rochester, a Co-PI may be a person in a training status, e. g., a fellow or resident who is conducting the study, but cannot, by University policy, serve as the Principal Investigator. Co-Principal Investigators might have synergistic contributions and have equal responsibility for the study conduct. For example, if there are both qualitative and quantitative activities, one person might be primarily responsible for the one and the other for the other, with the two sharing equal responsibility for the overall study.

Note: The HSPP/EPRP number and the

		expiration date will not be updated until the current form is being saved.
1.6	**Sub-Investigator(s):** (*Individuals who assist PI or Co-PI in certain assigned aspects of the study*) Last / First / Organization / HSPP/EPRP No. / Expiration Date Lyda, Elizabeth, Medicine, 77900113H, 1/31/2011 Mack, Cynthia, Medicine, 35650709, 7/20/2010 Pietropaoli, Anthony, Medicine, 10710604, 6/18/2010 Utell, Mark, Medicine, 15421105, 11/20/2012 Vora, Rathin, Environmental Medicine, 83461213H, 12/31/2011 **If applicable, list all non-UR affiliate Investigator(s) include Name and Institution:** **Submit a copy of the Human Subjects Investigator certification (or UR HSPP # for those institutions that do not provide such training.)** name / Revision / Modified Date There are no items to display	*"Subinvestigators" are those individuals who assist the PI or Co-PI in certain assigned aspects of the study. This equates to functions of "key personnel" on grant applications. NIH defines key personnel as those "who contribute substantively to the scientific development or execution of a project. Key personnel contribute a specified level of time (in contrast to others)." Typically, these are people who will be authors/co-authors on resulting study publications because of their contributions and work on the study.* *While the study plan/protocol should explain the role(s) of personnel who have contact with subjects or perform specific functions in the research, not all these persons should be listed in the application. For example, statisticians, phlebotomists, clinicians (providing clinical care), administrators and so forth should not be listed in the application although their involvement would be described in the study plan/protocol.* *Note: The HSPP/EPRP number and the expiration date will not be updated until the current form is being saved.*
1.7	**Study Coordinator** / **HSPP/EPRP** / **Expiration Date** * Erika Little / 75520812H / 8/31/2010	*This is the person who coordinates with the Principal Investigator and RSRB about the review and approval of this study. Along with PI and co-PI, this person also gets notify when an inquiry/ request being sent from the RSRB.* *Note: The HSPP/EPRP number and the expiration date will not be updated until the current form is being saved.*
1.7.1	**Additional Study Coordinator:** Last / First / Organization / HSPP/EPRP No. / Expiration Date There are no items to display	*Additional study coordinator(s) can be listed. This group is not being notified when an inquiry/request being sent from the RSRB.*

1.8	* Who will be the primary contact for questions or correspondence? Study Coordinator If **other**, provide name and phone No.:	
* Required field		

RSRB No.: RSRB00030395

2. Conflict of Interest

2.1.1	* Do any study personnel, spouses or dependent children receive or expect to receive **income for licensing discoveries** from the sponsor; or have an interest in a **patent, copyright or licensing agreement** whose value may be affected by this research? no	. *Office of Technology Transfer*
2.1.2	* Do any study personnel, spouses or dependent children have an **ownership interest** or serve in a **management capacity** or on the Board of Directors of the sponsor/company? no	
2.1.3	* Do any study personnel, spouses or dependent children hold or expect to hold **stock, stock options, or similar financial instruments** from any company which may be affected by the outcome of this research? no	*Mutual funds that are not actively managed by you/ your dependents are **not** included.*
2.1.4	* Do any study personnel, spouses or dependent children receive or expect to receive **financial compensation** from any company which may be affected by the outcome of this research (other than through a contract to the University to conduct this research)? no	
	If **Yes to any of the above**: Include a management plan (or waiver) signed by your Dean. Possible conflicts of interest should be reviewed by your Department Chair first. **Attachment:** *Note that disclosure of the conflict in the consent form should be a part of the plan or waiver. Also consider whether other actions would protect human subjects such as changes in recruitment, consent and safety monitoring procedures.*	. *UR Conflict Disclosure Form* . *Policy on Conflict of Interest* . *UR COI Reporting Form*
2.2	* Does the University have any institutional conflicts of interest in this study? no	*Institutional conflicts might be present if the University owns stock, stock options or other financial interest in the sponsor/ company.* *University Policy on Institutional Conflicts of Interest*
	If ***Yes:*** Explain:	

form #

RSRB No.: RSRB00030395

3. Source of Funding/Sponsorship (Grants and contracts must be submitted to the Office of Research and Projects Administration (ORPA).)

3.1 Please indicate Sponsor Type and Name:

no **No Funding or Sponsor**

no **Department Funding**
Department Name:
If other, please indicate:

yes **Government Agency**
Government Agency Name: NIH - National Institute of Environmental Health Sciences (NIEHS)
If other, please indicate:

Click Add to upload the government grant:

name	description
3167662.PDF	

Government Sponsored Grant Number:
RC1 ES018519

no **Foundation**
Foundation Name
If other, please indicate:

Click Add to upload the foundation grant:

name	description
There are no items to display	

Foundation Sponsored Grant Number:

no **Industry Initiated**
Company Name:
If other, please indicate:

no **Industry: PI-Initiated**
Company Name:
If other, please indicate:

*"**No Funding or Sponsor**" means that you are receiving no monetary or other support. Studies where a company supplies the test article (e.g., drug/ placebo) at no cost ARE considered to be sponsored.*

*"**Department Funding**" means that you are receiving some type of monetary support from one or more University departments (e.g., training funds, 'seed' money, etc.).*

*For "**grant-funded studies**", submit the entire grant, including the face page.*

RSRB No.: RSRB00030395

7. Just-In-Time (JIT) Study Part 1

7.1	* Is this a Just In Time (JIT) study? ○ Yes ◉ **No**	*Just In Time (JIT) only applies to NIH or certain Foundation studies. For more information, please call RSRB office.*

form #

RSRB No.: RSRB00030395

6. Project Funding

6.1	* Is the UR a sub-contractor of this grant? no	
	If ***Yes:*** Name of principal grantee:	
6.2	* Will the sponsor provide monetary support? [Industry sponsored studies may incur review fees.] yes	
6.3	* Will the sponsor provide free drug and/or device? no	

form #

RSRB No.: RSRB00030395

8. Coordinating Center Studies, Concept Studies and Umbrellas

No subject enrollment or access to subject data is allowed under a Coordinating center, Umbrella, or Concept study. All research activities involving human subject enrollment or subject data collection must be submitted separately for review.

8.1	* Is this a multi-site study for which the University of Rochester is the Coordinating Center (i.e., subjects will enrolled by other "site" investigators)? no	***Coordinating Center:*** *provides administrative oversight for a study conducted at one or more sites. No subject intervention.* *Note: For Coordinating Centers, be sure the protocol provides a description of the administrative activities that will be performed, including a description of information/data management activities.*

23

8.2	* Is this a "Concept Study," i.e., the protocol is in development and no subjects will be enrolled nor will any data be collected until approval of the final protocol? no	***Concept Study:*** *an idea (concept) for a study submitted to the RSRB (for grant requirement) prior to the complete protocol. Subject enrollment is pending review and approval of the protocol and consent form.*
8.3	* Is this an "Umbrella Study," i.e., does this study provide funding for sub-studies, but no subjects will be enrolled or data collected under this study itself? no	***Umbrella Study:*** *provides funding for separate studies, each of which undergoes RSRB review and approval. No subject intervention.*

form #

RSRB No.: RSRB00030395

9. Study Exemption

9.1	* Do you think this study may qualify as exempt under one of the federally recognized exemptions? no	*Except for taste and/or food quality evaluation, FDA regulated studies are **not** eligible for exemptions.* *Study exemptions must be granted by the RSRB. Exemptions may include, for example, "non-sensitive" and/or anonymous surveys, anonymous retrospective record reviews, and certain classroom evaluation activities. For more information about types of activities that qualify for exemption, click here.* ***Exempt studies carry a moral requirement to inform subjects, even if a formal research consent is not required.*** *Subject Information Sheet template* ***To assist investigators who need documents for non-English-speaking individuals, the RSRB has a Translator Declaration.*** *Submit the declaration to confirm the accuracy of wording in a foreign language document.*

24

* Required field	

form #

RSRB No.: RSRB00030395

49. Drugs, Devices and Biologics

49.1	* Will the study be using drugs, devices or biologics? no	

form #

RSRB No.: RSRB00030395

61. Student Projects

61.1	* Is this study a student project? no	
	If ***Yes:*** Indicate what type of project: no Undergraduate Project no Master's Thesis no Doctoral Dissertation no Post-Doctoral Project no Resident/Fellowship no Medical Student Project **If other, please indicate below:**	

form #

RSRB No.: RSRB00030395

62. Institutional Oversight/Cooperative Approvals

62.1 * Does this research proposal require review by any of the following University of Rochester committees? yes

If ***Yes*** check **all** that apply. Unless otherwise noted, a copy of committee approval is required prior to RSRB approval.

no CTO [Clinical Trials Office] approval is required for hematology/oncology related studies proposed at the University of Rochester and its affiliates. Contact the Clinical Trials Office at 585-275-5345 for instructions. (***Note**: if the PI works for the Cancer Center, this option should be checked. Do not uncheck it.)*

yes GCRC [General Clinical Research Center] (If any part of the study is conducted at or uses any resources of the GCRC)

Note: RSRB review will not begin until GCRC approval is given.

no Perinatal Research Committee (for studies involving pregnant women and newborns/infants in the normal nursery or neonatal intensive care unit at Strong Memorial Hospital or Highland Hospital. Contact Tel. 275-7480)

no ED Research Committee (For study involving the emergency department, emergency department patients, or members of the department of emergency medicine. Contact Telephone: 463-2970)

no Institutional Biosafety Committee (IBC)

For studies involving:

- 1. Introduction of recombinant DNA (plasmids) or gene transfer vectors (including viral vectors) into human subjects;
- 2. Introduction of genetically engineered micro-organisms or infectious agents into human subjects (including live vaccines if they are experimental in nature or not FDA-approved for use in the specific human study population);
- 3. The analysis of, or experimentation with, sera, blood products, or other specimens derived from humans in any UR lab that is not accredited within the College of American Pathologists (CAP) or the Joint Commission on Accreditation of Healthcare Organizations (JCAHO).

Contact the Institutional Biosafety Committee at 5-3014 or 5-2402.

no Surgical Pathology Approval (Required for use of slides or tissue from the Pathology Department)

no HURC/RDRC ('Radiation Safety') Committee approval required for human use of radioactive materials or ionizing radiation-generating devices for research purposes. Contact Tel. 5-1473.

☐ RCBI [Rochester Center for Brain Imaging] (If any part of the study is conducted at the RCBI,

CTO approval

CTO approval is required if the PI or Co-PI is Hematology/Oncology faculty (including non-malignant hematology) OR if the study involves cancer patients (regardless of the PI or Co-PI's department)

	contact e-mail rcbi_rsrb@rcbi.rochester.edu) no Other: **If other, please indicate below:**	

form #

RSRB No.: RSRB00030395

1. GCRC - General Information

(If you have any questions regarding section 72 (Parts 1, 2 and 3) please contact the GCRC directly at 275-6409)

1.1	Click **Add** to upload a document contains the description of the project: CUSP Summary(0.01) The 'Description of the Project' section, consisting of 250 words or fewer in text format, should be written in lay language. Background, rationale for the project, study question(s), design, study population, and outcome measures should be included. This segment will be publicly available through CRISP, so it should not contain any proprietary or confidential material.	*General Instructions*
1.2	Has this protocol received funding as of this GCRC submission? yes	
1.3	Projected start date: 1/4/2010	
1.4	Does this study evaluate a disease that would qualify as a Rare Disease or condition as defined by the NIH? no	*Rare disease or condition refers to any disease or condition that either:* 1. *Affects less than 200,000 persons in the United States, or* 2. *Affects more than 200,000 individuals in the US and for which there is no reasonable expectation that the cost of developing and making available within the US a drug for such a disease or condition will be recovered from sales of said drug or other therapeutic agent.*
1.5	Expected duration of study from initial enrollment to completion of last subject: 2 year(s)	
1.6	Outreach plans to ensure appropriate representation of women and minorities is obtained: Targeted subject recruitment if necessary.	

1.7	Are children (**under the age of 21**) are to be included? yes If **No**, reason for exclusion of children - (Check all that apply) *Notes: if "No", at least one box must be checked.* no The research topic is irrelevant to children. no Laws or regulations bar the inclusion of children. no Information being sought is already available for children or will be provided in another study. no A separate, age-specific study in children is warranted or preferred. no Not enough information is available regarding risk in adults to judge the potential risks in children. no Study is aimed at providing additional information on a previous all adult study. no Other special cases: the GCRC Advisory Committee will judge on an individual case-by-case basis. Describe:	*Click here for more detail about the question*
1.8	Please justify **WHY** GCRC resources are needed: Multiple blood draws, overnight stay, low-nitrate diet, procedures to be performed on GCRC.	
1.9	Is this an AIDS-related study? no	
1.10	Is this a multicenter trial? no	
1.11	Is this a clinical trial? no	
1.12	Data and Safety Monitoring Plan (DSMP): To help us review your protocol and determine where essential elements are included, please indicate on which page (or pages) they can be found in the protocol or grant application <u>Data Collection and Monitoring</u> Data to be collected (plan of study) and records to be kept (e.g. case report forms): Page(s) Protocol, pages 5-8; grant, page 44 Data Monitoring Page(s) Protocol, page 10 <u>Safety Monitoring/Adverse Events (AE) and Serious Adverse Events (SAE) Reporting</u> Who is responsible for monitoring safety (i.e. PI, safety monitor, DSMB, etc.) Pages Protocol, page 12	*Click here for more detail about the question*

Plan for safety review; when SAEs and AEs reported, and to whom (e.g. RSRB, DSMB, GCRC, etc.)

Pages
Protocol, page 12

Does the protocol include an AE grading and attribution scale?

If Yes, please indicate where this can be found.

Page(s)
No

Is there a Data and Safety Monitoring Board (DSMB) or Committee (DSMC)?

If Yes, please indicate where the description of the composition of the board (names of members or specialties represented), its duties, and the DSMB/DSMC charter (if available) is located.

Pages
No

form #

RSRB No.: RSRB00030395

2. GCRC - Participant Projections

2.1 Please project the number of ***new*** subjects for each GCRC grant year (March 1st to February 28th of each year) and then provide the total number for the duration of the study.

	Inpatient	**Outpatient**
1st year	10	
2nd year	26	
3rd year		
4th year		
5th year		
Total:	36	

2.2	Are subjects to be studied as inpatients? yes If **Yes**: **Per Subject**: number of days per admission: 2 Number of admissions: 2 Total days required: 4 Will these inpatients be seen on the GCRC: yes If **No**, where will they be seen?	*Definition of an inpatient admission day: the subject will be in a GCRC bed at midnight.*
2.3	Are outpatient visits included in study? yes If **Yes**: **Per Subject**: number of visits: 2 Approximate length of visit: 3 hours Total hours per subject: 6 Will these outpatients be seen on the GCRC? yes If **No**, where will they be seen?	

form #

RSRB No.: RSRB00030395

3. GCRC Services

Please indicate if the following services are needed:

3.1	NURSING SERVICES: yes If **Yes**, check all that are needed: yes Routine patient care (i.e. ht, wt, vital signs) no Special cardiac monitoring yes EKG no Biopsies Type of Biopsy: no Non-serial blood collections	

	yes Serial blood collections no Heparin-locks no IV lines no Renal vein sampling no IV infusions no 24 hour urine collections no Stool collections no Other, specify:	
3.2	OTHER SERVICES: If **Yes**, check as needed, and indicate the # of tests per subject no Bio-electrical impedance #/subject no Resting metabolic rate #/subject no Skin-fold measurement #/subject no DEXA scans #/subject (lumbar spine, hip, forearm, whole body, AP/lateral) no Other list:	*DEXA scans can be done for the following: lumbar spine, hip, forearm, and whole body.*
3.3	NUTRITION SERVICES: yes If **Yes**, check all that are needed: no Regular meals or snacks no Standardized meals no Metabolic or constant diet no Computerized dietary analysis (i.e. food records, 24 hr recall, food frequency) no Pre-admission counseling for dietary control (i.e. high carbohydrate diet prior to OGTT)	*If nutrition services are required beyond regular meals or snacks, contact the Nutritionist, Pat Stewart, PhD, RD, or the Nutrition Supervisor, Robin Peck, DT, at 275-3918, at least one month prior to the first patient visit/admission.*

	no Patient nutrition counseling/education yes Other (i.e. find appropriate nutrition assessment tools) List: low nitrate diet	
3.4	CORE LABORATORY SERVICES: no If **Yes**, please click the Add button below to list the test(s) Core Lab Listing There are no items to display	*The core lab does not have CLIA certification, so patient care decisions should not be made based on core lab tests.*
3.4.1	Is special handling of samples required? no If **Yes**, please explain: Other:	
3.4.2	Is another lab also processing blood samples? yes If **Yes**, what lab is being used? SMH Clinical Laboratory	*Please note: Investigators or coordinators are responsible for shipping samples to labs outside of SMH. The Core lab can provide space in the storage freezers to store samples prior to shipment. Please contact Noya Rackovsky at 273-4920.*
3.5	ANCILLARY SERVICES: no If **Yes**: Please complete for all ancillary tests you are requesting to be paid from the GCRC grant by clicking on the Add button below. Ancillary Lab Listing There are no items to display Are non-routine ancillaries requested (e.g. expensive drugs)? no If **Yes**, please justify why these are not to be charged to the funding agency. If the procedures are not listed, please include them with their associated cost:	*The NIH mandates that resources provided by the NIH for ancillary support only be used when no other support is available.*

3.6	INFORMATICS CORE: no If **Yes**: A) Resources Requested: no Automated data entry/verification processes no Database design, development, and management no Customized software creation and support no Streamlined data quality and management reporting no Internet-related solutions (i.e. Web applications, Web page development, Internet access to data) no Computer facility usage (3 PCs, network printer, scanners) no Other: B) Estimated data storage time: First entry of data: Analyses to be completed: C) Data collection for the project: no To be initiated no In progress no Already completed If **No**: Please indicate which of the following will be utilized instead: no Investigator PC yes Biostatistics no Drug Company	[redacted]

	no Other, describe:	
3.7	BIOSTATISTICAL ASSISTANCE: no If **Yes**: no Project design no Data analysis no Other list: Biostatistician on the Project (if already contacted): David Oakes	

form #

RSRB No.: RSRB00030395

63. Study Site(s)

63.1	* Will this research be conducted at Highland Hospital? no	*Highland Hospital is part of the URMC. However, consent form language (Compensation for Injury section) is specific to Highland Hospital.* *Please note that all studies that are to be conducted at Highland Hospital must be reviewed and approved by the HH Administrative Research Review Committee before enrolling subjects.*
63.2	* Will this research be conducted at any non-UR facilities? no If ***Yes:*** **List the name of facilities and contact persons:** **Click Add to upload the IRB approval or the letter of cooperation:** name description There are no items to display	*Note: Submit a copy of the IRB approval for each site. If the site has no IRB, a 'letter of cooperation' from the director of the facility where research will be conducted should be submitted. Special instructions may apply for federally funded projects - consult the RSRB.*

form #

RSRB No.: RSRB00030395

73. Cross Referencing Studies

73.1	* Is this the same protocol as another study, but includes a different funding source? no If ***Yes***, list RSRB#:	
73.2	* Is this study similar to another study, but has protocol modifications? no If ***Yes***, list RSRB#:	
73.3	* Is this a re-submission of a previously closed study? no If ***Yes***, list RSRB#:	
73.4	* Is this being funded or supported as part of another study? no If ***Yes***, list RSRB#:	*An example is a study that is covered/ funded under an umbrella grant or a under a grant that provides funds for training projects.*
73.5	* Is this application part of a 'Five-year review'? no If ***Yes***, list RSRB#:	*Except for studies that are only conducting data analysis, the RSRB requires resubmission including an updated protocol every five years.*
73.6	* Is this a submission to convert from a paper file? no If ***Yes***, list RSRB#:	

form #

RSRB No.: RSRB00030395

74. Use of Specimen(s)

74.1	* Will this study use only stored or discarded tissue, blood and/or other biological specimen(s)? no	*Link to the federal Office for Human Research Protection Guidance on Research Involving Coded Private Information or Biological Specimens*
74.2	* Will any fetal tissue or stem cells be used in this study? no	

form #

RSRB No.: RSRB00030395

35

64. Subject Population

Note: Include **all** groups of subjects (for example children, parents/guardians, teachers, Providers, students, staff members) about whom information will be collected.

64.1 Will this study involve direct contact with study subjects? yes

64.2 Will this study involve access to subject records, specimens or information? yes

For example, review of private records or medical charts, specimen samples or other subject data.

64.3 * What is the Total Number of Research Subjects expected to be enrolled (or their records/specimens accessed) at the sites for which you are **RESPONSIBLE**? 80

Note: For all numeric data fields, **DO NOT** include commas.

The number of subjects is the total of subjects involved in the research. For example in a study that needs 100 subjects to complete the study and expects that 20 subjects will drop out after enrolling (starting) should request at least 120 subjects total. In the same study, if a screening procedure will be used that involves subject interaction or use of identified data from 200 potential subjects to

	Number of Subjects at UR Site(s)	Number of Subjects at Non-UR Site(s)
Experimental Group (Treatment, Intervention, Interaction)	80	
Control Group (Non-Intervention, Placebo)		
Total Number of Subjects	80	

UR Subjects (or Subject Records /Specimens)			
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	4	4	8
Not Hispanic or Latino	36	36	72
Ethnic Category Total of All Subjects [1]	40	40	80

Racial Category			
American Indian/Alaska Native	0	0	
Asian	4	4	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	4	4	
White	32	32	

Racial Category Total of All Subjects [1]	40	40	

[1]The Ethnic Category Total of All Subjects must be equal to the Racial Categories Total of All Subjects.

Only complete this table if you're enrolling subjects at non-UR sites.

Non-UR Subjects (or Subject Records /Specimens Used)			
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino			
Not Hispanic or Latino			
Ethnic Category Total of All Subjects [1]			
Racial Category			
American Indian/Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American			
White			
Racial Categories Total of All Subjects [1]			

[1]The Ethnic Category Total of All Subjects must be equal to the Racial Categories Total of All Subjects.

identify the 100/120 who will be asked to join, then the total number reported on this page (and explained in the study plan/ protocol recruitment section) should be 200.

The number of subjects (n) is important to the ethical review of studies because it is a measure of research risk exposure. The number in your application (i. e., what is entered on this page) must agree with the number in your study plan/ protocol. The number of subjects also relates to scientific validity and thus to the risk/ benefit determination that must be made to approve the study. Please be as accurate

as possible; however, the board does understand, and can work with approximations when necessary. When a study is approved, it is approved for a maximum subject enrollment equal to the number entered on this page. It is very important that, if you believe that you will subsequently exceed this number, you submit an amendment to increase your sample size to cover the extra subjects; such amendments must be approved before involving subjects beyond the previously approved number.

If this is an 'umbrella', 'coordinating center' or

		'concept' study (I.e. there is no subject enrollment or data collected from subject records/ specimens under this protocol), enter '0' for the Total Number of Research Subjects in 64.3.
64.4	Indicate the age ranges for subjects. Check **all** that apply and submit appropriate forms. (Note: exempt studies generally do not require written consent): no 0-6 years [Parent/Guardian Permission form required] no 7-12 years [Parent/Guardian Permission form and verbal child assent script required] no 13-17 years [Parent/Guardian Permission form and written child assent form required] yes Adults: 18 years and older [Consent form(s) required] no Adults over age 89 [Consent form(s) required]	*Knowing the age range of potential subjects is important to the ethical review of studies because adequate provision must be made for soliciting consent and the assent of children capable of providing a meaningful agreement. This University follows, in general, the "rule of 7s" when considering assent requirements for children. That mans that, while determined on a study-by-study basis, children under the age of 7 are not asked for assent; teen aged children are asked to sign written assent; and, those*

		children in between are asked for oral assent (no signature). Involvement of persons who are 90 or more has implications under the HIPAA regulations (i.e., the age becomes an identifier).

RSRB No.: RSRB00030395 *form #*

75. Vulnerable Populations (to be Targeted)

75.1 Check **all** that apply:

	no Minors (Under 18 years)	yes Employees	no Nursing Home Residents	*This question asks about the primary subject population/populations. If a study is designed with no restrictions (i. e., a "general population" study), then check the "None" box. Note that children and prisoners may NOT be enrolled in general population studies – special RSRB approval is required by federal regulation. If the study does seek to enroll vulnerable populations specifically, then check all that apply.*
	no K-12 students	no Pregnant women	no Limited or non-reader	
	no UR students (under 18 years)	no Prisoners	no Mentally compromised	
	yes UR students (18 years and over)	no Terminally Ill (life expectancy less than 6 mos.)	no Economically Disadvantaged	
			no None	

75.2 Are there enrollment restrictions based on:

Race? no	Ethnicity? no	Pregnancy? yes	*This question asks about exclusion of subjects. The most common exclusion is for children because many studies are not appropriate for their enrollment. If pregnant women are excluded, justify why this is necessary, as they should not be excluded without rationale.*
Gender? no	Age? yes	HIV Status? yes	

If *answer above is* ***Yes*** to **Pregnancy** or **HIV Status**, will you test prospective subjects for?

- Pregnancy? ◉ **Yes** ○ No
- HIV status? no

75.3	Provide scientific rationale for restricting or including any of the populations indicated in questions **75.1** or **75.2:** **People over age 60 will be excluded because of the possibility of confounding health issues.** **Pregnant people will be excluded because of unknown risks to the fetus.** **HIV patients will be excluded because HIV affects immune cells.**	*Undue influence may occur when a potential subject is in a dependant relationship, (e.g., students or patients) or in a special situation/ circumstance (e.g. desperately ill patients, prisoners, etc.) State what procedures will be put in place to ensure that subjects are given the opportunity to independently decide not to participate.*
75.4	Describe how undue influence and coercion will be minimized for these subjects and how precautions will be used to protect the rights and welfare of these subjects: Students or employees under the direct supervision of the investigators will not be included.	*Undue influence may be encountered when the person asking for consent/ enrollment is in a dependant relationship, (e.g., students or patients) or in a special situation/circumstance the desperately ill, prisoners, etc. The description should state what procedures will be put in place to ensure that subjects are enrolled without any external pressures.*
75.5	Will decisionally impaired adult subjects or those of questionable capacity to consent be included? no If ***No***: All subjects must give their own consent to be enrolled in the research (unless consent is waived). If ***Yes***: Explain briefly how capacity will be determined, who will make that determination, how the process will be documented and who will provide permission for incapacitated subjects: *Note: Provide a complete description of these procedures in the Protocol.	*There is no universally accepted test or standard for making a determination of capacity for research consent. This process should be described in the study plan/protocol and operate in much the same manner as the informed consent process. The determination is based upon the potential subject's ability to respond to the process appropriately. Some investigators ask questions such as (or use a form that asks): naming at least two potential risks of participating in the study; stating things that he/she will be expected to do during the study; asking the subject to explain what he/she would do if he/she no longer wanted to participate; and asking the subject to explain what he/she would do if he/she experienced distress or discomfort during the study. The person who obtains consent should ensure that the subject is alert, able to communicate, able to understand information about the research, make a decision based upon the information, and give informed consent.*

75.6	Does this study evaluate a disease that would qualify as a Rare Disease or Condition as defined by the NIH? no	*An orphan or rare disease is generally considered to have a prevalence of fewer than 200,000 affected individuals in the United States.*
75.7	Will this study enroll children based upon permission from *non-parental* guardians? no	*Researchers must verify or confirm that the guardian has been duly appointed as a guardian pursuant to state law. This may be accomplished by, for example, obtaining (and maintaining in the study subject's file) a copy of the court order (or other legal appointment document) appointing the person as guardian. The researcher must confirm that the guardian's authority applies to granting permission for medical care/ research and is not limited to just financial matters.*
75.8	If children are involved in the research: Does the study involve treatment? no If Yes, is this treatment available only in the context of research (explain):	*Treatment available only in the context of the research may apply to the study as a whole or to a specific portion or portions of the study.*

RSRB No.: RSRB00030395

65. Non-English Speaking Part 1

65.1	* Will any non-English speaking subjects be included in this study? no	*Please note, that "non-English speaking subjects" also includes persons who use sign language (e.g., ASL) to communicate.*
65.2	If ***Yes***: Have you included both English and non-English versions of all subject documents (i.e. consent forms, written questionnaires, information or recruitment letters)?	*Documents may be translated by a fluent individual or a professional translation service. SUNY Binghamton offers translation services at Tel. 607-777-6765 or email trip@binghamton.edu.*

65.3	If non-English speaking subjects will be included: describe how you will provide information in a language understandable to the subject or authorized representative.	

form #

RSRB No.: RSRB00030395

66. Subject Recruitment or Use of Subject Records/Specimens

66.1 Check **all** methods of recruiting subjects (or methods of collecting subject data/specimens) for this study:

yes Poster	no Information Letter[1]	yes Brochure or Flyer
no Radio or TV Ad	yes Email or Internet[1]	yes Newspaper
no Clinic or Private Practices[1]	no Referrals[1]	no Medical Records[1]
no School/Day Care Records[1]	no Psychology sign-up bulletin	no Telephone Script
no Psychology Research Pool [PRP]		no Other: **If other, provide method below:**

[1] Initial subject contact must be from treating clinician or referral source.

A final copy of all audio/video taped advertisements and comercially printed advertisements must be submitted after the RSRB has approved the copy to be used. This will be a stipulation for final RSRB approval and transmitting the approval letter.

Upload Recruitment Materials:
Important: If you're revising or replacing the previously uploaded document, use the **Replace** link next to the file name. Do not delete any document after the study has been submitted to the RSRB.

name	Revision	Modified Date
CUSP Newspaper	0.01	11/18/2009 9:45 AM
CUSP Internet	0.01	11/18/2009 9:45 AM
CUSP Flyer	0.01	11/18/2009 9:45 AM

IMPORTANT! *Use the 'Add' button to upload new (i.e. previously not submitted) documents only. To make changes to a document that has already been submitted to the RSRB, use the 'Replace' link.*

Example: If the study has been submitted and the RSRB sends the application back to your 'Inbox' and asks (a) for you to revise your recruitment brochure and (b) that you include a recruitment letter, proceed as follows:

1. *Go to the Upload Recruitment Materials section (66.1) and use the 'Edit' link to upload the revised version of your brochure.*
2. *Use the 'Add' button to upload the not yet submitted recruitment letter.*

66.2	* Will subjects be recruited in person for this study? no If ***Yes***: Explain who will approach potential subjects to take part in this study and the circumstances of the recruitment process. Be sure to fully address privacy issues, i.e., how you will protect the privacy of potential subjects:	*Privacy is the freedom from unauthorized intrusion/disclosure. i.e., the state of being let alone and able to keep personal information to oneself.*
66.3	* Are subjects chosen from private medical, psychiatric or academic records? no	*Example 1: **Investigator has routine access** to the private medical, psychiatric or academic records and needs to access these records in order to obtain data from the subject's private records for this research purpose.*
	If ***Yes***, Do any investigators on this study have routine access to the records?	*Example 2: **Investigator does not have routine access** to the private medical, psychiatric or academic records and needs to access these records in order to obtain data from the subject's private records for this research purpose. (Initial subject recruitment must 1st come through 'treatment team' or individual with routine access.)*
66.4	* Does this study include subject chart or record review only? no	

form #

RSRB No.: RSRB00030395

67. Subject Payment/Incentives

67.1	* Will subjects receive any payment/incentive for participation? yes If ***Yes***, Describe. Include payment schedule, if applicable. Subjects will be paid $100 after completing Visit 1, $350 after completing Visit 3, and $350 after completing Visit 5, for a total of $800. **[Include in both the protocol and the Consent form(s)].**	*Payment for study participation must be pro-rated based on the duration of participation. Completion of the study may not be a requirement for payment.* *Click here for the Finance Department's policy regarding payment to research subjects: http://www.rochester.edu/adminfinance/finance/subjects.html*

67.2	Specify form(s) of subject payment: no Cash yes Check no Gift certificate no Other: **If other, provide type of payment or incentives below:**	

form #

RSRB No.: RSRB00030395

77. Risks and Benefits

77.1	Check any applicable possible risks or potential harms to subjects:	
	no Use of deception yes Physical injury or discomfort yes Stress no Manipulation of psychological or social variables such as social isolation or psychological stresses yes Discovery of previously unknown condition (e.g. disease, suicidal intentions, depression, genetic predisposition): Specify condition and explain how this knowledge will be handled: Testing done at screening could discover an unknown condition. If that happens, the patient will be informed and advised to seek medical attention, and the testing information will be provided to the patient and the health professional that they request be informed. yes Invasion of subjects privacy no Invasion of privacy of individuals other than the subject no Risk to reputation or risk of financial harm no Social or legal risk yes Materials that may be sensitive, offensive, threatening or degrading no Other risks: If other risks, describe:	

77.2	* Describe the protections that will be implemented to minimize risks or harms of **all** items checked: It is very unlikely that these exposures to concentrated outdoor particles will cause symptoms or clinically important effects. Similar studies are currently ongoing, using the same Harvard ultrafine particle concentrator, at the U.S. Environmental Protection Agency. They have nearly completed a study in healthy subjects and have found no adverse effects. Our previous studies of exposure to UFP at 50 µg/m3, with intermittent exercise, were without adverse effects. This study will be conducted at rest, which will further reduce the particle dose. In a separate study ("Inhaled particle characteristics and early lung effects," RSRB #8126), healthy subjects have been exposed to ultrafine and fine zinc oxide particles at a concentration of 500 µg/m3 without adverse effects. Previous human studies of exposure to fine carbon particles found no clinical effects of exposure to 250 µg/m3 for 1 hour or 500 µg/m3 for 2 hours. The National Ambient Air Quality Standard for outdoor particulate matter in the air (PM2.5) is 65 µg/m3, averaged over 24 hours. There is a small, theoretical risk of precipitating a cardiac event in persons with severe coronary artery disease. Therefore, subjects will have a screening ECG read by a cardiologist prior to exposure. Nevertheless, it is possible that subjects recruited for this study could have clinically silent cardiovascular disease, that might not be detected by the screening examination and ECG. We feel that the risk for precipitating a cardiac event in these exposures is extremely small, even for a subject with unrecognized coronary artery disease. First, the particles used in this study will be outdoor particles similar to what people breathe every day. The number concentrations will be higher than people usually inhale in Rochester, but will be similar to what people breathe when driving on a busy highway, or working in certain occupations. Second, all exposures will be conducted at rest, as opposed to our previous studies in healthy subjects, which have generally involved exercise. Thus the actual dose of particles to the lung will be lower in this study, and the cardiovascular stress of exercise will be absent. Finally, the risk of cardiovascular events associated with outdoor air particles is relatively small, and has required studies of millions of people to detect. While this risk is important from a public health standpoint, the net increase in risk for individuals on any given day of exposure remains very small. For example, Peters et al. found in a study of residents in the Boston area, an odds ratio for MI of approximately 1.3 associated with an increase in air pollution from the cleanest days to the worst days. The age-adjusted incidence of first acute MI for adult males is approximately 10 per 1,000 person-years, or 10 per 365,000 person-days. Thus, according to the Peters data, the risk of having a heart attack related to the worst air pollution day in Boston would increase from 1 in 36,500 to 1 in 28,077. The risk would be lower for people without clinical evidence of coronary artery disease. Given that the exposures used in this study are for only 2 hours rather than a whole day, the risk of precipitating a cardiovascular event is extremely small. The subject will be under direct observation by a trained investigator at all times during the exposure. Monitoring facilities provide continuous measurements of particle concentrations. Symptoms and sensitive measurements of pulmonary function will be monitored before and after exposure. Exposures will be discontinued if any adverse symptoms occur. All subjects will remain in the Clinical Research Center for approximately 6 hours after exposure and symptoms will be assessed before discharge. Finally, subjects will return approximately 24 hours after each exposure to assess possible delayed effects. The human exposure facility is located in MRBX, a short walk from Strong Memorial Hospital. Physician availability is assured at all times.	
77.3	* Describe the anticipated benefits of this research (Do not overstate): Information gained from this research will increase our understanding of the mechanisms for the health effects of air pollution particles, and aid in the determination of appropriate air quality standards.	

78. Data Safety Monitoring Board (DSMB)

78.0	Describe the data and safety monitoring plan: The subject will be under direct observation by a trained investigator at all times during the exposure. Monitoring facilities provide continuous measurements of particle concentrations. Symptoms and sensitive measurements of pulmonary function will be monitored before and after exposure. Exposures will be discontinued if any adverse symptoms occur. All subjects will remain in the Clinical Research Center for approximately 6 hours after exposure and symptoms will be assessed before discharge. Finally, subjects will return approximately 24 hours after each exposure to assess possible delayed effects. The human exposure facility is located in MRBX, a short walk from Strong Memorial Hospital. Physician availability is assured at all times.	*A data and safety monitoring plan is required for all studies involving greater than minimal risk. The plan may be as simple as the investigator monitoring each subject for any distress, problems etc., or it may need to be more complex with external monitors for certain types of studies.*
78.1	* Will this study use a Data Safety Monitoring Board? no If Yes, provide contact information [1] for the DSMB:	*A data safety monitoring board (DSMB) or data monitoring committee (DMC) is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical trial. The DSMB/DMC advises regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial. The link below is to an FDA document that is intended to assist in determining when a DSMB/DMC is needed for optimal study monitoring, and how such committees should operate.* *http://www.fda.gov/ohrms/dockets/98fr/010489gd.pdf* *[1] Contact information means who can RSRB call (email) if RSRB want to discuss something about data/safety monitoring.*
78.2	* Will an independent monitor (e.g. NCI, sponsor) audit this study? no	*Independent Monitors perform "on site" monitoring of individual case histories, assess adherence to the protocol, ensure the ongoing implementation of appropriate data entry and quality control procedures, and in general assess adherence to good clinical practices.*

form #

81. Procedures and Billing

81.1	* List the research procedures and indicate who is billed for **each procedure:** physical examination - completed by study team investigator (no bill) spirometry - completed by study coordinator (no bill) pregnancy screening - bill study grant blood draw - CRC nursing staff will perform service (no bill) blood clinical labs - bill study grant ECG - CRC nursing staff will perform service (no bill) DLNO - completed by study team lab technician (no bill) DLCO - Pulmonary Function Lab bills study grant	*If these questions do not apply to your study, enter 'n/a'.*
81.2	* List the standard of care procedures and indicate who is billed for each procedure: N/A	
81.3	* List procedures that delay or preclude standard of care treatment: N/A	

form #

RSRB No.: RSRB00030395

68. Confidentiality of Data, Including Recording and Photographs

68.1 Check types of subject identifiers that will be collected for this research. Check **all** that apply.

yes Name	yes Address	yes Telephone No.
yes E-mail Address	no Fax No.	yes Zip Code
no Account No.	no Medical Record No.	no Health Plan Beneficiary No.
no License No.	no License Plate No.	no Certificate No. [Including Device Serial No.]
no Audiotapes	no Videotapes	yes Social Security No.[1]
no Subject Code	no Website URL Address or Internet IP Address	
no Finger or Voice Prints	no Full face Photographs/ Images	
no Student ID number		
yes Dates [Such as birth date, date of death, admission or discharge date]		

	no None of the above [No identifiers will be collected]	
	[1]Indicate specific purpose for use of Social Security Numbers (note that the study must comply with the UR policy for use of social security numbers in a research database http://www.rochester.edu/it/policy/SSN-PII/): Required for IRS reporting of $800 payment.	
68.2	If any identifiers are checked, explain how you will protect against disclosure of these identifiers: Data will be recorded in bound laboratory books. Only the investigators and technicians directly involved in data acquisition and analysis will have access to the data. Samples and data will be coded to protect the identity of the subjects. Computers and data books will be stored in a locked laboratory.	*Although related, the concepts of privacy and confidentiality are different. Confidentiality means the ethical and/or legal right that information, such as research data, will be held secret and safeguarded from disclosure unless consent is provided permitting disclosure. (Privacy is the freedom from unauthorized intrusion/disclosure. I.e., the state of being let alone and able to keep personal information to oneself.)*
68.3	* Explain how long you will keep this research data and how you will store/secure the data: Data will be kept indefinitely, under secure lock and key or password protected.	
68.4	* Will any non-study personnel (including the sponsor) have access to subject data? yes If ***Yes***: Specify: University of Rochester and the U.S. Environmental Protection Agency.	
68.5	* Does this study involve "genetic testing"? yes If ***Yes:*** Contact RSRB office for further information.	
68.5.1	* Does this study involve keeping the data/samples for possible future research studies (e.g. tissue banking)? yes If ***Yes***: Could the future research involve Genetic Testing? yes	

form #

RSRB No.: RSRB00030395

82. Federal Certificates of Confidentiality

82.1 * Will this study include a Certificate of[1] Confidentiality? no

If ***Yes***, provide the expiration date of the certificate:

Click Add to upload the Certificate of Confidentiality:

name	Revision	Modified Date
There are no items to display		

*[1]Although not routinely required, if the data collected contains information about illegal behavior, genetic or other sensitive information, you may wish to visit the NIH Certificates of Confidentiality website at **http://grants1.nih.gov/grants/policy/coc/** for information on how to obtain a Federal Certificate of Confidentiality. The RSRB may require you to obtain this certificate.*

form #

RSRB No.: RSRB00030395

83. Informed Consent Process

83.1 How will you obtain subject consent for this study?

yes **Written Consent: Attach copy of all consent/permission/assent forms.** Important: If you're revising or replacing the previously uploaded document, use the **Replace** link next to the file name. Do not delete any document after the study has been submitted to the RSRB.

name	Revision	Modified Date
CUSP Consent Form	0.02	11/20/2009 10:51 AM

Guidelines for Type of Consent Documents

***Adult subjects** (those 18 years or older) - Provide Consent Form*

***Child subjects** (those 13 to under 18 years) - Provide a Parental Permission Form + an Assent Form (include signature of minor)*

***Child subjects** (those 7 to under 13 years) - Provide a Parental Permission Form + an Assent Script (no signature of minor)*

***Child subjects** (those under 7 years) - Provide a Parental Permission Form. Assent form or script not required.*

	no **Verbal Consent: Include request for waiver of documentation of consent.Attach written scripts for verbal consent/permission/assent.** Important: If you're revising or replacing the previously uploaded document, use the **Replace** link next to the file name. Do not delete any document after the study has been submitted to the RSRB. name Revision Modified Date There are no items to display	*Checking 'yes' for Verbal Consent will require information for requesting a Waiver of Documentation of Consent. The opportunity to provide this information will pop up on the next screen, after the 'Continue' button is clicked.*
	no **Consent for Deception Study.** Attach the following: no **Consent to Procedures** and no **Consent for Use of Data** name Revision Modified Date There are no items to display	*Note that 'deception studies' are most commonly used in the field of psychology. If the study involves deception (i.e. the study subject will not know the true purpose of the research at the time of enrollment), then two documents are required, the 'Consent to Procedures' (for enrollment) and the 'Consent for Data Use' (for debriefing).*
	no **No Consent and/or Parent Permission: Include a request for waiver of consent and/or waiver of parent permission.**	*By checking 'No Consent' will require information for requesting a Waiver of Consent. The opportunity to provide this information will pop up on the next screen, after the 'Continue' button is clicked.*
83.2	* Describe the steps that will be taken to minimize undue influence and coercion We will not recruit subjects under the influence of the investigators (student, patient, employee). After the screening visit, subjects will be given a copy of the consent to take home and they can choose to withdraw at any time.	*Minimizing undue influence is important for all research with human subjects, but especially so when the investigator has a prior relationship with potential subjects (e.g., teacher-student, caregiver-patient, etc.). Steps might include: a mandatory waiting period between informing the potential subject and obtaining consent; having someone other than the person (s) with the prior relationship obtain consent; having an advocate for potential subjects; etc.*
* Required field		

85. Informed Consent Process Part II

85.1	* Will anyone other than personnel listed on page 1 obtain consent for this study? no If **Yes**, list name(s), HSPP or EPRP number(s) and expiration date(s):	*The University assumes that the persons listed on page one of this application (I. e., the principal investigator, co-investigators, sub-investigators and the study coordinator) can and will be enrolling subjects and obtaining consent. Persons obtaining consent must have appropriate training and knowledge of the study to perform this important function. The protocol (study plan) should outline the process for obtaining consent; specifying who, where, when and how.*
85.1.2	* Will the consent form be given to subject or authorized representative to read prior to discussing the consent in detail? yes	
85.1.3	* Will the subject or authorized representative be allowed to take the consent form home, if requested, to discuss with family members? yes	
85.1.4	If you answered ***No*** to ***Q85.1.2, Q85.1.3,*** explain:	*The federal regulations require that the consent process provides the prospective subject or authorized representative sufficient opportunity to consider whether to participate. One way this might be addressed is a waiting period between the discussion and the enrollment/start of research procedures.*

form #

RSRB No.: RSRB00030395

70 Part 1. Use of Protected Health Information (PHI)*: HIPAA Requirements

70.1	* Is your department/organization considered a University of Rochester "covered entity"? yes	*The covered entities included in the URMC/Strong Health affiliated designation are:*
		• *The University of Rochester's healthcare components: (see Policy 0P15.1)*
		  ○ *Strong Memorial Hospital*
		  ○ *Eastman Dental Center*
		  ○ *School of Medicine and Dentistry*
		  ○ *School of Nursing*
		  ○ *University of Rochester Medical Faculty Group*
		  ○ *University Health Service*
		  ○ *Mt. Hope Family Center*
		• *Highland Hospital of Rochester*
		• *The Meadows at Westfall, Inc. (Highlands at Brighton)*
		• *Highlands Living Center, Inc. (Including Meadowbrook)*
		• *Laurelwood at Highland*
		• *Medical Administrative Associates, Inc. (Highland Apothecary)*
		• *Visiting Nurse Service of Rochester and Monroe County, Inc.*
		• *Community Care of Rochester*
		
		URMC/Strong Health Policy

70.2	* Is the PI or any other study personnel part of the "covered entity"? yes	

form #

RSRB No.: RSRB00030395

70 Part 2. Use of Protected Health Information (PHI)*: HIPAA Requirements

** PHI is defined as individual health information that: (1) is created or received by a health care provider, health plan, employer or health care clearinghouse; and (2) relates to the past, present or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present or future payment for the provision of health care to an individual.*

70.3	* Will you collect any subject PHI * as part of this study? yes If ***Yes***: Indicate how you will comply with the HIPAA Requirements for this study. Check one of the following:	*The Privacy Rule defines PHI as individually identifiable health information, held or maintained by a covered entity or its business associates acting for the covered entity, that is transmitted or maintained in any form or medium (including the individually identifiable health information of non-U.S. citizens). This includes*
	no De-identification of Data[1]	

no Limited Data Set and Data Use Agreement[2]	*Identifiable demographic and other information relating to the past, present, or future physical or mental health or condition of an individual, or the provision or payment of health care to an individual that is created or received by a health care provider, health plan, employer, or health care clearinghouse. For purposes of the Privacy Rule, genetic information is considered to be health information.*
yes HIPAA Authorization [Include HIPAA language in consent form(s) and specify that subjects will receive a signed copy of the consent/authorization.]	
no Waiver of HIPAA Authorization [Include a request for a Waiver of HIPAA Authorization].	
[1]*Refer to URMC/Strong Health Policy OP25, Page 6, Item #5 (Requires URMC Username and Password)*	
[2]*Refer to URMC/Strong Health Policy OP25, Page 7, Item #6 (Requires URMC Username and Password)*	

form #

RSRB No.: RSRB00030395

Important: *If this application is not yet complete, leave the selection 'No' below. This will save the information you have entered to date and allow you to log back in and complete the application at a later time. If the application is complete, change the selection to 'Yes' below. Remember that completing the application does not mean it is submitted, just that you are done with entering information.* *** Is this Application completely filled out? yes**	
Does your department conduct on-line review and approval of studies? yes **For Departments that Do Conduct On-line Review** *When the PI presses the 'Submit Application' buttons, the completed application and attachments (uploaded files) will be forwarded electronically to your designated department reviewer.* **Note:** *If you have not uploaded all documents (e.g. protocol, grant, etc.) to the application, you will need to supply those in hard copy to the department reviewer and the RSRB.* **For Departments that Do Not Conduct On-line Review** *You will need to print the application (using the 'Print View' button) and send it and all hard copy documents to your department reviewer. After departmental sign-off, the PI can press the 'Submit/OK' buttons to submit the application to the RSRB. The signed department' approval (including hard copies of all documents not uploaded in the online system) must then be submitted to the RSRB.*	*This field shows whether or not your department conducts online review*

form #

RSRB No.: RSRB00030395

Final Instructions

Clicking the 'Continue' button below, will take you back to your workspace. Your study will be in the '**Pre-Submission**' stage. Here you will be able to view the application in two ways. The 'View/Application Form' button takes you page by page through the application. Click the 'View/Print Application' button to view the entire application using the scroll tool or to print the application. In the '**Pre-Submission**' stage, you may also go back into the application (using the 'View/Application Form' button) to add attachments (upload documents) or modify your responses.

Submission

Once complete and ready for submission, the Principal Investigator must click the 'Submit' button. Once the application has been submitted, the application becomes 'read-only', i.e. you will not be able to access the application to make changes. Revisions or additions can only be made if the Department Reviewer or the RSRB sends the application back to you for changes.

Remember! The RSRB review process does not begin until department approval (either online or written) has been received.

form #

Consent Form

Study Title: Cardiovascular Effects of Ultrafine Particles in Genetically Susceptible Subjects ("CUSP")

Principal Investigator: Mark W. Frampton, MD

Introduction:

This consent form describes a research study and what you may expect if you decide to participate. You are encouraged to read this consent form carefully and to ask the person who presents it any further questions you may have before making your decision whether or not to participate.

This study is being conducted by Dr. Mark Frampton of the Pulmonary and Critical Care Medicine Division of the Department of Medicine at the University of Rochester Medical Center.

You are being asked to participate in this study because you are a healthy nonsmoker 18 to 60 years of age.

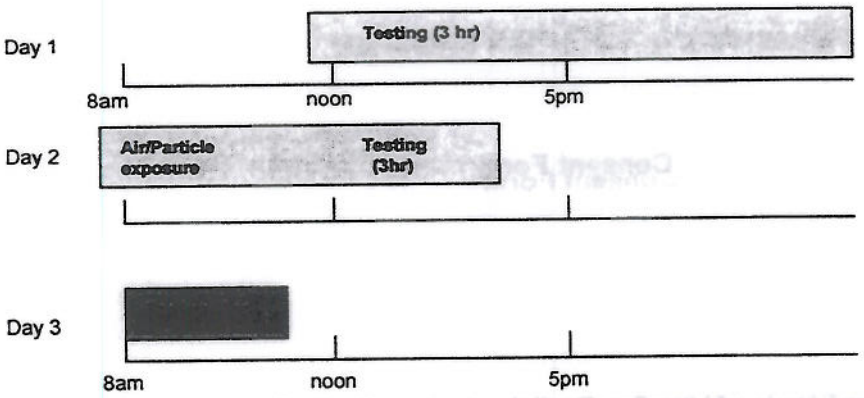
Purpose of Study

The purpose of this research study is to determine whether people exposed to very small ("ultrafine") particles normally present in the outdoor air develop temporary changes in their lungs or blood vessels. We are also testing whether people with a specific kind of genetic makeup are more susceptible to these temporary effects. The levels of pollutants to which you will be exposed will not be higher than what you could be exposed to if you visited many major cities around the world.

If you agree to participate in this study, you will be asked to come to the Clinical Research Center (CRC) on 5 separate days, including 2 overnight stays, for a total of about 57 hours over approximately 6 weeks.

Visit 1 (Screening) takes 2-3 hours.

Visits 2, 4 are overnight visits (□). Visits 3, 5 (■) are 3-hr follow-up visits. *The 2 overnight visits take place at least 3 weeks apart.*



At the screening visit (Visit 1), you will complete a standardized questionnaire for assessment of respiratory symptoms and medical history. We may access your medical records if necessary to confirm eligibility for the study. You will have a medical and physical examination, routine breathing tests (spirometry), an electrocardiogram (ECG), and a blood test, including genetic testing. The amount of blood to be drawn will be 1-2 tablespoons. A pregnancy test will be performed in female subjects. The pregnancy test must be negative. Visit 1 will determine whether you are eligible to continue in this study. After Visit 1 has concluded, we will test your blood for genes that might affect how the body protects itself against air pollution. It is important that we have people with different forms of these genes taking part in this study. It is possible that the results of testing, including the type of gene you have, will make you ineligible for this study. We require that some of the blood sample be saved to be used for other research in the future. Samples will be identified only with your initials and a number, not your name.

You must be able to avoid the medications listed below, for 1 week before starting the study, until the study period is finished:

- Ibuprofen, naproxen, and aspirin
- Prednisone
- Vitamins C and E
- Antihistamines
- Anti-oxidants
- Fish oil
- Niacin
- Arginine
- Over-the-counter decongestants

During Visit 1 you will be instructed in a special diet that is low in nitrates. You will be given a list of both appropriate foods and those to be avoided. You will be asked to start this diet at dinner the evening before your overnight visits (Visits 2, 4) and continue until the end of the 3-hr follow-up visit (Visits 3, 5). You will also be asked to avoid caffeine when you are actively involved in the study, starting with dinner the evening before the overnight visits (Visits 2, 4). You will also be asked to avoid strenuous exercise and heavy lifting when you are actively involved in the study, starting the day before the overnight visits (Visits 2, 4)

One or more days after Visit 1, you will be asked to come to the CRC at 11:30 am (**Visit 2**). *You will be rescheduled if you have experienced an upper or lower respiratory tract illness within the past 6 weeks, or any other acute illness within the past week.* Women will be asked about their latest menstruation and a urine pregnancy test will be conducted. If you are pregnant your participation in the study will end and you will receive full compensation for the exposure day. You will be given lunch. At about 12:30 pm you will have the following procedures: blood pressure, heart rate, oximetry (a finger clip attached to measure oxygen in your blood), a questionnaire about symptoms, urine collection, spirometry, and removal of blood from a vein (3-4 tablespoons) and an artery in your arm (less than 1 tablespoon). We require that some of the blood sample be saved to be used for other research in the future. Samples will be identified only with your initials and a number, not your name. Adhesives will be placed on your neck and side of your chest to measure your heart function (impedance cardiography), and then we will measure blood flow in your forearm before and after inflation of a blood pressure cuff on your upper arm (reactive hyperemia). Finally, we will measure the movement of inhaled nitric oxide and carbon monoxide (lung diffusion). This testing will take about 3 hours. You will be given dinner that evening, and will stay on the CRC overnight.

The next morning you will have a light breakfast at 6:30 am. At 7:15 am you will be transported by wheelchair to the Kornberg Medical Research Building. You will then have a 2-hour exposure to either clean air or clean air containing concentrated outdoor ultrafine particles. You will not be told which exposure you are receiving, and the investigators will not know. Only the person operating the exposure equipment will know which exposure is being given. The order of giving air or particles will be chosen at random (like flipping a coin).

The exposure will be done inside a Plexiglass chamber (6 x 5 x 3.5 ft, 98 cubic feet). The chamber will be under negative pressure, which may make your ears pop, like going down in an elevator. On the particle exposure day, the air you breathe will contain particles from outside the building that have been concentrated about 10 to 20 times more than their concentration outdoors. The number of particles that you will be exposed to will depend on the amount of pollution in the outdoor air on the day of your exposure. A trained investigator will be nearby to observe you at all times. A physician will be on call in the facility during the entire exposure period.

It is not expected that the exposures in this study will cause any symptoms. If it appears you are experiencing any problems, or you develop any symptoms of discomfort, the exposure will be stopped immediately. In addition, you may choose to stop the exposure at any time for any reason. If you do so, you will be paid in full for that day's session, but will be ineligible for further participation in the study and for any further payments.

After the exposure, we will record your blood pressure, heart rate, oximetry, and symptoms. You will be transported back to the CRC to perform spirometry. You will be given lunch at 11:30 am. At about 12:30 pm you will have the following procedures: blood pressure, heart rate, oximetry (a finger clip attached to measure oxygen in your blood), a questionnaire about symptoms, urine collection, spirometry, and removal of blood from a vein (3-4 tablespoons) and an artery in your arm (less than 1 tablespoon). We require that some of the blood sample be saved to be used for other research in the future. Samples will be identified only with your initials and a number, not your name. Adhesives will be placed on your neck and side of your chest to measure your heart function (impedance cardiography), and then we will measure blood flow in your forearm before and after inflation of a blood pressure cuff on your upper arm (reactive hyperemia). Finally, we will measure the movement of inhaled nitric oxide and carbon monoxide (lung diffusion). This testing will take about 3 hours. All of these measurements are described in detail below. You will then go home. The total time for Visit 2 will be about 29 hours.

You will return the next morning (**Visit 3**) at 8:00, approximately 24 hours after exposure. You will have the following procedures: blood pressure, heart rate, oximetry (a finger clip attached to measure oxygen in your blood), a questionnaire about symptoms, urine collection, spirometry, and removal of blood from a vein (3-4 tablespoons) and an artery in your arm (less than 1 tablespoon). Adhesives will be placed on your neck and side of your chest to measure your heart function (impedance cardiography), and then we will measure blood flow in your forearm before and after inflation of a blood pressure cuff on your upper arm (reactive hyperemia). Finally, we will measure the movement of inhaled nitric oxide and carbon monoxide (lung diffusion). This testing will take about 3 hours. You will then go home.

At least 3 weeks after Visit 2, you will return for **Visits 4 and 5**. The procedures performed on Visits 2 and 3 will be repeated. You will have completed the study after Visit 5.

The measurement procedures are described below:

1) **Routine breathing tests (spirometry).** This test requires you to perform 3 to 5 forceful exhalations after a deep breath. This test is performed routinely on patients and does not carry significant risks.

2) **Urine collection.** Urine samples will be collected in a small plastic container. These samples will be stored and used to look for products that might change in response to the particle exposure.

3) **Blood drawing.** Blood will be removed from a vein in your arm once during the screening visit (visit 1), twice during the overnight visits (visits 2 and 4), and once during the follow-up visits (visits 3 and 5) for the study of blood cells and fluids. This means that you will have 3 blood draws each week for the 2 weeks that you participate in the study (once a day for 3 days). The amount of blood taken at each blood drawing will be less than 4 tablespoons (50 ml) at a time, no more than 250 ml over the 3 visits of an exposure session, and no more than 500 ml over the whole study. In this study, we require that blood samples be stored for possible additional future research. These samples will be labeled with a code, not your name.

Blood will also be collected from a small artery in your forearm twice during the overnight visits (visits 2 and 4) and once during the follow-up visits (visits 3 and 5) for the study of blood cells and fluids. This means that you will have 3 arterial blood draws each week for the 2 weeks that you participate in the study (once a day for 3 days). The amount of blood taken at each blood draw will be no more than 1 tablespoon (15 ml). This will be done using a standard technique that is also used every day with patients in and out of the hospital. A small needle is passed through the skin and into an artery in your forearm. Blood is collected into a syringe, the needle is withdrawn, and then a bandage is applied. The pressure inside arteries is higher than it is inside veins, so it is important to hold pressure over the needle site to prevent bleeding. This usually means that we have to apply firm pressure with our fingers on top of the bandage for several minutes.

4) **Heart function test (impedance cardiography).** This test is like an EKG, and measures how hard your heart is working. Skin patches are placed on the sides of your neck and chest, and a recording is taken for about 5 minutes. There is no discomfort or risk from this test.

5) **Blood flow test (reactive hyperemia).** This involves a blood pressure cuff to be applied to your wrist and another to your upper arm. A tube will be wrapped around your forearm to measure its size. The blood pressure cuff above your elbow will be partially inflated so that the volume of blood entering the forearm in a measured period of time can be calculated. The cuff will inflate and deflate for one minute, at least 5 times for multiple

measurements. The cuff will then be inflated above the blood pressure in your arm for 5 minutes, during which time your arm will tingle. The cuff is then released and measurements are taken as the blood returns to your arm. This will take about 30 minutes.

6) **Measurement of lung diffusion.** These are two tests that measure how quickly certain gases get into the lung. The first test measures the diffusing capacity for carbon monoxide, or DLCO. This is part of routine breathing tests and involves inhaling air with tiny amounts of carbon monoxide and helium, holding your breath for 10 seconds, and then breathing out. The second test measures the diffusing capacity for nitric oxide, or DLNO. Nitric oxide is a gas that is produced and released in very small quantities by many cells in the body. You will inhale a low concentration (up to 10 parts per million) of nitric oxide from a bag and then hold your breath for 3-5 seconds followed by a slow exhalation. This will be repeated 2 times. This concentration of nitric oxide is higher than is found in fresh air, but is below the levels that have been measured in air that is normally found in the stomach or in the sinus of the nose. The concentration is also below that which is commonly used for medical treatment of various lung diseases. The concentration of nitric oxide in your exhaled breath is also measured. You will hold your breath for 10 seconds and then breathe out at a constant rate while we measure the nitric oxide in this exhaled breath. This is repeated two times. There are no known undesirable effects from these tests.

7) **Measurement of lung volumes.** Measurement of lung volumes is also part of routine pulmonary function testing, and will be performed once prior to the first exposure. The subject enters a body plethysmograph, a Plexiglas box with dimensions similar to a phone booth. You will pant against a shutter while measurements are recorded to calculate lung volume. The test requires up to 15 minutes and is a standard clinical test performed in pulmonary function laboratories.

The table below shows when these procedures will be performed.

	Visit 1 (Screening)	Visit 2 (Overnight)	Visit 3 (Follow-up)	Visit 4 (Overnight)	Visit 5 (Follow-up)
History and Physical Examination	X				
Blood Pressure, Heart Rate, and Oximetry	X	X	X	X	X
Symptom Questionnaire		X	X	X	X
Spirometry	X	X	X	X	X
Blood Drawing	X	X	X	X	X
Heart Function Test		X	X	X	X
Forearm blood flow Test		X	X	X	X
Lung Diffusion Tests		X	X	X	X
Pregnancy Test	X	X		X	
Air/Particle Exposure		X		X	
Lung Volume		X			

Number of Subjects

We expect to enroll approximately 80 subjects to participate in this study.

Risks of Participation

The particles you breathe will come from outdoor air pollution that we all breathe. The number of particles will be higher than normally occur outdoors in Rochester.

These concentrations of **particles** are not expected to cause any symptoms. Large epidemiology studies indicate that exposure to air pollution particles may increase the risk of having a heart attack or other heart problems in people who have heart disease. If you have symptoms such as chest pain or shortness of breath, the exposure will be stopped.

Breathing tests (spirometry) may induce lightheadedness as a result of taking a deep breath 3 times in a row.

Blood drawing may cause pain and bruising at the place where the blood is taken. Rare complications from blood drawing include, but are not limited to, blood clots, infection, and light-headedness or fainting. The risk of pain, blood clots and bleeding from an artery are higher than after drawing blood from a vein. The risk is of bleeding is minimized by applying firm manual pressure for several minutes after the sample is taken.

Measuring the **exhaled nitric oxide** may cause drying of the nose or mouth.

Forearm blood flow test may cause temporary numbness of the hand and arm.

Lung diffusion testing may cause drying of the nose or mouth.

Questions on the health questionnaire will ask about smoking and drinking habits, which may make you feel uncomfortable.

Benefits of Participation

There are no benefits that you can expect to receive as a result of participating in this study.

Costs

There will be no cost to you to participate in this study.

Payments

You will be paid $100 after completing Visit 1, $250 after completing visit 2, $100 after completing visit 3, $250 after completing visit 4, $100 after completing visit 5, for a total of $800.

Sponsor Support

The University of Rochester is receiving payment from the National Institutes of Health and the U.S. Environmental Protection Agency for conducting this research study.

Compensation for Injury

If you are directly injured by the procedures solely required to participate in the study, you may need to pay for treatment of your injuries, but you will not be required to pay for emergency medical treatment provided at Strong Memorial Hospital or Highland Hospital. The University may seek payment for this care from your health insurer or third parties. Decisions regarding care and compensation for any other research related injury will be made on a case-by-case basis.

Confidentiality of Records and HIPAA Authorization

While we will make every effort to keep information we learn about you private, this cannot be guaranteed. Other people may need to see the information. While they normally protect the privacy of the information, they may not be required to do so by law. Results of the research may be presented at meetings or in publications, but your name will not be used.

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires us to get your permission to use health information about you that we either create or use as part of the research. This permission is called an Authorization. We will use your research record, and the results of procedures and measurements done for this research study.

We will use your health information to conduct the study and determine research results. We will monitor your health status and measure the effects of inhalation of particles. Health information is used to report results of research to sponsors and federal regulators. It may be audited to make sure we are following regulations, policies, and study plans. Strong Health policies let you see and copy health information after the study ends, but not until the study is completed. If you have never received a copy of the Strong Health HIPAA Notice, please ask the investigator for one.

To meet regulations or for reasons related to this research, the study investigator may share a copy of this consent form and records that identify you with the following people: the University of Rochester; the Department of Health and Human Services; National Institute of Environmental Health Sciences and the U.S. Environmental Protection Agency.

If you decide to take part, your Authorization for this study will not expire unless you cancel (revoke) it. The information collected during your participation will be kept indefinitely. You can always cancel this Authorization by writing to the study investigator. If you cancel your Authorization, you will also be removed from the study. However, standard medical care and any other benefits to which you are otherwise entitled will not be affected. Canceling your Authorization only affects uses and sharing of information after the study investigator gets your written request. Information gathered before then may need to be used and given to others.

As stated in the section on Voluntary Participation below, you can also refuse to sign this consent/Authorization and not be part of the study. You can also tell us you want to leave the study at any time without canceling the Authorization. By signing this consent form, you give us permission to use and/or share your health information as stated above.

Contact Persons

If you have any questions regarding this research, or if you believe that you have suffered from a research-related injury, emotional or physical discomfort, you should contact Dr. Mark Frampton at (585) 275-4161.

If you have any questions about your rights as a research subject, or any concerns or complaints, you may contact the Human Subjects Protection Specialist at the University of Rochester Research Subjects Review Board, Box 315, 601 Elmwood Avenue, Rochester, NY 14642-8315, telephone (585) 276-0005; for long-distance you may call toll-free, (877) 449-4441. You may also call this number if you cannot reach the research staff or wish to talk to someone else.

Voluntary Participation

Participation in this study is voluntary. You are free not to participate or to withdraw at any time, for whatever reason, without risking loss of present or future care you would otherwise expect to receive. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner.

Signature/Dates

Study Subject:

I have read (or have had read to me) the contents of this consent form, and have been encouraged to ask questions. I have received answers to my questions. I agree to participate in this study. I have received (or will receive) a **signed** copy of this form for my records and future reference.

_____**PRINT NAME**

_____**SIGNATURE** _____**DATE**

Person Obtaining Consent:

I have read this form to the subject and/or the subject has read this form. I have given the subject adequate opportunity to read the consent before signing. The subject will receive a **signed** copy of this consent form. An explanation of the research was given and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information.

_____**PRINT NAME AND TITLE**

_____**SIGNATURE** _____**DATE**